DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Ethoprop

Chemical Code # 404, Tolerance # 262
SB-950 # 93

July 24, 1986
Revised: 1/26/87, 7/1/87, 5/9/88, 6/2/88, 3/23/89, 10/5/89, 11/20/90, 12/11/91, 5/24/93, 6/10/94, 3/8/95 and 4/9/98

I. DATA GAP STATUS

Combined (chronic & onco), rat:	No data gap, no adverse effect.
Chronic toxicity, dog:	No data gap, possible adverse effects.
Oncogenicity, mouse:	No data gap, no adverse effect.
Reproduction, rat:	No data gap, possible adverse effects.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome:	No data gap, possible adverse effects.
DNA damage:	No data gap, possible adverse effect.
Neurotoxicity:	No data gap, no adverse effect.

Toxicology one-liners are attached.

All documents through volume136 record #'s: 159626 and 962372 were reviewed.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name:T980409
Revised by H. Green and S. Morris 12/11/91; M. Silva, 5/24/93, 6/10/94 & 3/8/95; Gee, 4/9/98

See also EPA "Guidance for the Reregistration of Pesticide Products Containing Ethoprop as the Active Ingredient," June, 1988.

These pages contain summaries only. Individual worksheets may contain additional effects.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

** 102, 104 118435, 127458 "104-Week Combined Chronic Toxicity and Carcinogenicity Study with Ethoprop in Rats", (Williams, K.D., Hazleton Laboratories America, Inc., Madison, WI., Report # 6224-151, 10 September 1992). Ethoprop technical (95.6% pure) was administered *ad libitum* in the diet for 104 weeks to Crl:CD®(SD)BR VAF/Plus® rats (80 or 90/sex/dose) at 0 (Purina Certified Rodent Chow® #5002 meal), 1, 60, and 400 ppm (reduced from 600 ppm during week 3 due to toxicity in females). Chronic NOEL = 60 ppm (Tremors in females were increased and body weights were significantly decreased (7% to 20%) at 400 ppm. Thyroid, spleen, kidney and liver weights were decreased, while testes weights were increased at 400 ppm.) No adverse effect: Oncogenicity NOEL > 400 ppm (The study was previously evaluated as having a NOEL = 60 ppm (Silva, 5/20/93), based on an apparent positive trend for endometrial stromal benign polyps in females (400 ppm) at terminal sacrifice. In addition, there was a positive trend for C cell carcinoma and malignant pheochromocytoma in males and endometrial stromal polyps in females at 400 ppm.) After evaluation of information submitted by the registrant, the tumors can be considered age-related, rather than specifically due to ethoprop. ChE NOEL = 1 ppm (reduced plasma (47% to 82% inhibition), RBC (25% to 51% inhibition), and brain (28% to 65% inhibition) ChE values at 60 and 400 ppm in both sexes.) **Acceptable**. (M. Silva, 6/3/94).

262-029 962357, "Evaluation of the Chronic Toxicity and Oncogenic Potential of Ethoprop in Fisher 344 Rats," (GSRI Project No. 413-858-41, 01/20/83; Gulf South Research Institute, New Iberia, LA, 1/20/83). Ethoprop, 95.3%; dietary exposure of F_0's to 0, 60.5, 131, or 262 ppm for 8 weeks prior to mating thru weaning of F_1 pups; dietary exposure of 60 F_1's/sex/dose to 0, 4.5, 9, or 18 ppm for weeks 0 - 12, then 0, 49, 98 or 196 for weeks 13 - 109; F_0's discarded; 10 F_1's/sex/dose necropsied at 52 weeks, remaining F_1's necropsied at 109 weeks; dose-related decreases in food consumption, body weight, and survival may be due to pre- and neo-natal exposures; MTD based on cholinesterase depression in females at 196 ppm (serum 7% and brain 35 % of control); **possible adverse effect** indicated at 196 ppm by increased incidences of thyroid C-cell adenomas in males and uterine proliferative lesions in females; study UNACCEPTABLE and not upgradeable (pre- and neo-natal exposures complicate interpretation of adult chronic effects, dose levels changed at 3 months, no 6- or 18-month clinical chemistries, no ophthalmoscopic examinations, no NOEL for cholinesterase inhibition). (Gee, 4/15/85; Morris, 02/16/88).

EPA one-liner: Supplemental, additional data required - no NOEL for cholinesterase inhibition, 6/88. The reregistration standard requested a special study in rats to determine the NOEL for cholinesterase inhibition.

262-030 thru -034; 962358 thru 962362. Addenda to 262-029; 962357. Individual data.

262-067; 058184. Addendum to 262-029; 962357. Missing pages and registrant's statements (dated 06/13/87 and 06/23/87) about CDFA's [DPR] evaluation of study.

262-069 058186, "Lifetime Dietary Toxicity and Oncogenicity Study in Rats", (International Research and Development Corporation, Mattawan, MI, 04/30/85). Ethoprop, 94 - 96%; 0, 1.0, 10, or 100 ppm in the diet of 70 Fischer 344 rats/sex/dose for 24 months; 10 rats/sex/dose

necropsied at 12 and 18 months; no dose-related clinical signs; NOEL = 1.0 ppm (cholinesterase inhibition - plasma and erythrocyte at 10 and 100 ppm, brain at 100 ppm); no dose-related pathological effects; **no adverse effect indicated**; study UNACCEPTABLE and not upgradeable (MTD not reached). (Morris/B Davis, 12/29/87, 02/16/88).

EPA One-liner: Core Supplementary, 1/26/89.

CONCLUSION:

The report in 102/118435 contends that the thyroid tumor incidence is higher at 400 ppm since these animals showed greater survival than controls and therefore the lesions had more time to increase in size. Thyroid changes (hyperplasia, adenoma and carcinoma), it was stated, are common age-related changes (the older the animal, the greater the occurrence). The endometrial polyps were also discounted in the report since they are considered to be benign and non-aggressive. Endometrial polyps are also considered to be age-related and therefore the increased occurrence at 400 ppm was expected. Although this information may be true, it is not possible to discount these lesions because they also were observed in an earlier study reviewed at DPR (DPR volume/record #: 262-029/962357).

Incidence of Microscopic Observations - Terminal Sacrifice

	Treatment Levels (ppm)							
	0	49	98	196	0	49	98	196
	Males				Females			
# Animals Examined	47	43	44	46	44	46	39	44
THYROID								
C-cell Adenoma	3##	4	0	10	2	7	2	4
C-cell Carcinoma	1	1	0	1	0	3	3	4
UTERUS								
Endometrial Polyps					0##	4	8	13

- Significant by trend test at $p < 0.01$ (performed by the reviewer).

In this case, the survival was similar across all groups, yet there was still an increase in incidence of thyroid and uterine lesions in animals treated at 196 ppm. The effect of ethoprop on thyroid and uterus are thus considered to be treatment-related and not simply due to longer survival. M. Silva, 5/21/93.

CHRONIC TOXICITY, DOG

Subchronic Study:

262-088 086768, "A Five-Month Oral Toxicity Study with One-Month Recovery in Beagle Dogs with Ethoprop Technical", (N. N. Hamada, Hazleton Laboratories America, Inc., HLA Study No. 656-143, 4/11/90). Ethoprop technical (purity of 95.6%, lot #: 303019003) was administered by gavage in gelatin capsules at concentrations of 0 (corn oil in capsule), 0.01, 0.025, or 1.0 mg/kg/day to 6 Beagle dogs/sex/group for 20 weeks. **No adverse effect indicated.** CHE NOEL = 0.01 mg/kg/day (Plasma cholinesterase inhibition for males = 16.7% and females = 20.4%-25.6% at 0.025 mg/kg/day and males = 73.6%-77.1% and females = 74.7%-79.6% at 1.0 mg/kg/day. Erythrocyte cholinesterase inhibition in males = 20.4%-26.4% at 1.0 mg/kg/day.

Chronic NOEL > 1.0 mg/kg/day (No other treatment related observations were reported.) These data are supplemental. (Kishiyama & Silva, 10/16/90).

Chronic Study:

****262-054 048657**, "Ethoprohos 52 Week Oral (Capsule Administration) Toxicity Study in the Beagle" (HUK Project 198/16); Hazleton UK, North Yorkshire, England; 04/29/86). Ethoprop technical, 96.1%; by oral capsule in peanut oil at 10, 1, 0.025, or 0 mg/kg/day to 4 dogs/sex/dose for 1 year; **possible adverse effect** - hepatotoxicity: elevated SGPT, centrilobular vacuolation, focal necrosis, periportal fibrosis and biliary proliferation with 1 moribund at 10 mg/kg; centrilobular vacuolation only at 1 mg/kg; reduced RBC, HGB, and HCT at 10 and 1 mg/kg; NOEL = 0.025 mg/kg/day (hepatotoxicity); originally unacceptable; Martz, 01/20/87; upgraded to ACCEPTABLE by information at 262-068, 058185. (Morris/Parker, 02/22/88).
EPA: Core Supplementary. No repeat study required but a special subchronic study in dogs for a cholinesterase NOEL. 6/88 reregistration standard.

262-068 058185. Addendum to 262-054; 048657. Quantitation of dose and registrant's statements (dated 06/18/87 and 06/23/87) about CDFA's evaluation of study.

CHRONIC TOXICITY, MOUSE

262-071 062430, "Chronic Feeding and Oncogenicity Studies in Mice with Ethoprop," (Exp. # 94; Rhone-Poulenc Inc., Monmouth Junction, NJ; 12/29/84). Ethoprop, 94.6%; 0, 0.2, 2, or 30 ppm in diet of 80 mice/sex/dose for 104 weeks; 10 mice/sex/dose necropsied at 26, 52, and 78 weeks; maximum cholinesterase inhibition at 30 ppm, plasma Z 77%, erythrocyte Z 81%, brain Z 36%; no other dose-related clinical, pathological, or histological signs; no adverse effect indicated; study UNACCEPTABLE (no ophthalmologic examinations) and not upgradeable (no MTD) as a chronic toxicity study. (Morris/B. Davis, 01/12/88).

262-070 062623. Exact duplicate of 262-071 062430. Study was submitted to comply with FIFRA 6(a)(2) and contains registrant's statements (dated 9/24/87) about CDFA's evaluation of study.

262-071 062430. Also contains registrant's statements (dated 9/29/87) about CDFA's evaluation of study.

ONCOGENICITY, MOUSE

262-025-028, 962363-66, "Chronic/Oncogenic Evaluation of Ethoprop with B6C3F1 Mice", (FDRL, 1/26/83). Technical ethoprop (lot 2225-62) at 0, 15, 30, and 60 ppm in the feed for 18 months to 50/sex/group; ten-fold dosing error in week 54, causing excessive high dose mortality in weeks 55 and 56 (18 males and 9 females). Marked eye lesions (phthisis bulbi), especially in females, in all groups including controls. An extensive effort to determine the origin of this problem was unsuccessful. [Indicates diseased or defective mice, or husbandry problems (e.g. irritation from cage detergent) -F. Martz] Because of the ophthisis bulbi, the other ocular effects are difficult of evaluate. Optic nerve gliosis and eosinophilic bodies at 30 and 60 ppm. Gliosis in females: 3/59 (control), 10/57 (15 ppm), 15/60 (30) and 22/60 (60 ppm). No clear evidence for oncogenic effects, but second review found positive trend for preneoplastic hepatocellular lesions. Initially reviewed as UNACCEPTABLE and not upgradeable: study compromised by

uncontrolled/unknown factors, dosing error, and lack of an MTD, therefore insufficient information for oncogenic assessment. The six week study (see # 072723 below) justifies the dose of 60 ppm as adequate. (Gee, 4/15/85 and 3/23/89 and Martz, 6/30/87).

EPA one-liner: Supplemental based on lack of an MTD. The HDT was considered to be two times lower than the MTD. 6/88 reregistration standard.

Rebuttal located in #262-055.

262-055, No record #; Rebuttal to mouse oncogenicity study noted above (record #962363-66); narrative only with no supplemental information; no change in status. (Martz, 6/30/87).

262-078 072723, "Six Week Dietary Toxicity Study in Mice." (IRDC, 8/24/88, 347-032). Ethoprop technical, 95.9%, fed in the diet for 6 weeks at 0, 100, 200 or 400 ppm to 10/sex/group, B6C3F1 mice; purpose was to determine if 60 ppm in study #962363 was high enough; all animals died or were sacrificed at 400 ppm, 3/10 females died at 200 ppm; erythrocyte, plasma and brain cholinesterase were all inhibited at termination of survivors with brain at 37% and 28% of controls in males at 100 and 200 ppm respectively; at 41% and 32% at 100 and 200 ppm in females; food intake and body weights were lower at 200 ppm; ChE NOEL < 100 ppm (cholinesterase inhibition, clinical signs of tremor, decreased defecation). Supplementary data for dose justification for 962363-66. (Gee, 3/21/89).

**262-071 062430, "Chronic Feeding and Oncogenicity Studies in Mice with Ethoprop," (Exp. # 94; AN-PYO Center, Japan; 12/29/84). Ethoprop, 94.6%; 0, 0.2, 2, or 30 ppm in diet of 80 mice/sex/dose for 104 weeks; 10 mice/sex/dose necropsied at 26, 52, and 78 weeks; maximum cholinesterase inhibition at 30 ppm, plasma ≈ 77%, erythrocyte ≈ 81%, brain ≈ 36%; no other dose-related clinical, pathological, or histological signs; no adverse effect; study ACCEPTABLE as a mouse oncogenicity/carcinogenicity study only. (Morris/B. Davis, 01/12/88).

This study is not listed in the 1988 reregistration standard. (Gee, 3/22/89).

This study also contains registrant's statements (dated 09/29/87) about CDFA's [DPR] evaluation of study.

262-070 062623. Exact duplicate of 262-071; 062430. Study was submitted to comply with FIFRA 6(a)(2) and contains registrant's statements (dated 9/24/87) about CDFA's [DPR] evaluation of study.

262-077 067401, "Historic Control Data for B6C3F1 Mouse for the Chronic Feeding Oncogenicity Studies in Mice with Ethoprop", (Biosafety Research Center, AN-PYO Center, Japan, 12/84). Present submission contains historical control data on tumor incidences in B6C3F1 mice to supplement an original study that was submitted to comply with FIFRA 6(a)(2) (CDFA doc. #262-070, rec. # 62623; exact duplicate of 262-071; 62430). CDFA found the original study acceptable as a Oncogenicity/Carcinogenicity study only. The present submission contains no information to alter CDFA's finding of no adverse effect in the original study. (Morris/Parker, 06/02/88).

REPRODUCTION, RAT

262-023 962356, "Evaluation of Effects of Ethoprop on Reproductive Performance by a Three Generation Study in Fisher 344 Rats," (Project # 413-858-41; Gulf South Research Institute; 12/03/80). Ethoprop, 95.3%, lot # MCTR 15977; 0, 60.5, 131, or 262 ppm in diet; 10 males and

20 females/group; each male mated with 2 females; 2 litters/generation for 3 generations; all F1A, F2A, F3A, F3B weanlings, and F0, F1B, F2B adults necropsied; enzootic pneumonia; weight gain at 14 weeks of exposure of 262 ppm adults Z 10 - 20% of 0 ppm adults; **Possible adverse effects:** decreased fertility, mean litter size, and 21-day litter weights at 262 ppm, decreased 21-day pup viability at 262 and 131 ppm; NOEL = 60.5 ppm (decreased 21-day pup viability); UNACCEPTABLE and not upgradeable (intercurrent disease); Gee, 4/11/85; one-liner update. (Morris/Gee, 01/28/88).
EPA one-liner: Unacceptable - insufficient data to determine NOEL's, illness, other problems. 6/88 reregistration standard.

262-072 063205. Addendum to 262-023, 962356. Missing pages and registrant's statements (dated 09/01/87) about CDFA's evaluation of study.

****262-095 097499**, "Two-Generation Reproduction Study of Ethoprop Technical Administered in the Diet to CD® (Sprague-Dawley) Rats", T.L. Neeper-Bradley, Bushy Run Research Center, Export, PA., Laboratory Project ID 53-598, 6/6/91. Ethoprop technical (95.3% purity, lot #308187003) was tested in a reproduction study by continuous dietary exposure of 28 Sprague-Dawley rats/sex/group through 2 generations (F0, F1B) with 2 litters in the first generation (F1A, F1B) and 1 litter in the second (F2). Adult F0's were continuously exposed for 10 weeks then through two cycles (F1A, F1B) of mating, gestation, and lactation. Selected F1B weanlings were continuously exposed for 12 to 15 weeks then through one cycle (F2) of mating, gestation, and lactation. The F1A, F1B, and F2 litters were possibly exposed in utero and via mothers milk. The exposure levels were initially 0, 1, 30, or 300 ppm. Approximately one week after weaning the last F1A litter (week 19) the high dose was reduced to 150 ppm. Significant treatment-related effects on F0 adults at 300/150 ppm were decreased body weight gains for males (weeks 0 - 20) and for females during gestation and lactation (weeks 11 - 18). Terminal brain and plasma cholinesterase activities were significantly lower at 300/150 and 30 ppm in F0 and F1 adults. There was a 13% decrease in plasma cholinesterase activity in F1 adults males at 1 ppm (ChE NOEL < 1 ppm). F0 thyroid weights were reduced in males and females at 300/150 ppm. There were no significant treatment-related effects on fertility or fecundity indexes. A **possible adverse effect** was indicated by decreased pup mean birth weights (F1A, F1B) and weight gain (F1A, F1B, F2) at 300/150 ppm and decreased weanling survival at 300 ppm (F1A). The decreased weight gain for the F1B's at 300/150 ppm persisted through adulthood (reproductive NOEL = 30 ppm). The study was acceptable (H. Green and S. Morris, 12/9/91).
TERATOLOGY, RAT

**262-084 085900, "Teratology Study in Rats with Ethoprop - Final Report", (Rodwell, D.E., Springborn Life Sciences, Inc., SLS Study No. 3147.39, November 13, 1989). Technical ethoprop (purity = 95.6%, lot #: 303019003) was administered by gavage at dosage levels of 0 (corn oil), 2, 9, and 18 mg/kg/day to mated (a sperm positive vaginal smear or copulatory plug = day 0 of gestation) Sprague-Dawley rats (25/group) on gestation days 6 through 15. Maternal NOEL = 9 mg/kg/day (A significant reduction in bodyweight, bodyweight gain and food consumption was observed.) Fetal NOEL > 18 mg/kg/day (No evidence of fetal effects.) ACCEPTABLE. (Kishiyama & Silva, 10/17/90).

**262-023 962355, "Teratologic Evaluation of Ethoprop MCTR-603-78 in Sprague-Dawley Rats", (Laboratory No. 5850; Food and Drug Research Laboratories, Inc.; 04/24/79, amended 06/10/85). Ethoprop, 94% pure, in corn oil; 0, 0.16, 1.6, or 16 mg/kg/day by oral gavage on days 6 - 15 of gestation to 25 - 35 mated females/dose; maternal NOEL = 1.6 mg/kg (decreased weight gain and 21/35 died at 16 mg/kg); developmental NOEL = 1.6 mg/kg (decreased fetal

weight at 16 mg/kg); **no adverse effect** (developmental NOEL = maternal NOEL); initially reviewed as unacceptable but upgradeable with submission of individual fetal data and dose analysis. (Gee, 04/11/85 and Gee/Parker, 07/25/86). The possible adverse effect was changed to no adverse effect by information at 262-074, 063398. (Morris/Parker, 5/9/88). Data submitted in 262-079, individual fetal data, dosing preparation and stability of ethoprop in corn oil upgrades the study to ACCEPTABLE status. (Gee, 3/22/89).

EPA one-liner: Supplemental; teratology NOEL > 16 mg/kg (HDT); maternal NOEL = 1.6 mg/kg; possible embryotoxicity at 0.16 mg/kg. Historical control data required. 6/88 reregistration standard.

262-074 063398. Addendum to 262-023 962355. The amended report contains summarized fetal information and registrant's statements (dated 09/01/87) about CDFA's evaluation of study.

262-079 067594, 067595. Addenda to 962355 upgrading study to acceptable status. Volume contains individual dam and fetal data, records of dosing preparation and stability in corn oil. (Gee, 3/22/89).

TERATOLOGY, RABBIT

Rangefinding Study:

262-089 089020 "Rangefinding Teratology Study in Rabbits with Ethoprop," (Springborn Life Sciences, Inc., Spencerville, OH, 8/24/89; Study #: 3147.40). Ethoprop technical (95.6% pure; Lot #: 303019003, SLS Test Article ID #: S89.004.3147) was used at 0 (vehicle = Mazola corn oil), 0.1, 0.5, 2.0, 5.0 and 10.0 mg/kg (adjusted for active ingredient to 100%) on artificially inseminated New Zealand white rabbits (8/group) during days 6 to 18 of gestation (day 0 = day of insemination). **No adverse effect indicated. Maternal NOEL =** 2.0 mg/kg (Maternal deaths, clinical signs and decreased bodyweight gain were observed at $\geq$ 5 mg/kg/day.) **Developmental NOEL** $\geq$ 10 mg/kg (No effects were observed at any dose.) These data are supplemental. M. Silva, 11/16/90.

Teratology Study:

**262-085 085901, "Teratology Study in Rabbits with Ethoprop - Final Report", (Rodwell, D.E., Springborn Life Sciences, Inc., SLS Study No. 3147.41, November 15, 1989). Technical ethoprop (purity = 95.6%, lot #: 303019003) administered by gavage at dosage levels of 0 (corn oil), 0.625, 1.25, and 2.5 mg/kg/day to 20 artificially inseminated New Zealand White rabbits/group on gestation days 6 through 18 (insemination = day 0 of gestation). Maternal & Developmental NOEL > 2.5 mg/kg/day (No effects observed at any dose). ACCEPTABLE (An MTD was not achieved in this study, however the doses selected were justified, based on the range-finding study--089 089020.) (Kishiyama & Silva, 11/19/90).

**262-023 962354, "Rabbit teratology study Ethoprop technical - 01238101 - Final Report," (Hazleton (VA), 8/10/81). Ethoprop technical, 95.7% pure, by oral gavage in corn oil at 2.0, 0.5, 0.125, or 0 mg/kg/day to 17 New Zealand White rabbits/level on days 6-18 with cesarean on day 29 (insemination = day 0); weight loss/reduced gain @ 2.0 and 0.5 mg/kg during dosing period; no effect on uterine parameters; no dose-related or unusual malformations or variations. No adverse effect. Maternal NOEL = 0.125 mg/kg/day; NOAEL $\geq$ 2.0 mg/kg; developmental NOEL > 2.0 mg/kg/day. Original status unacceptable (Gee, 4/11/85), upgraded to complete and

ACCEPTABLE by rebuttal and supplemental information located in -055, 051591. (Martz, 6/17/87).
EPA one-liner: Unacceptable. Additional data required including historical control data. 6/88 reregistration standard.

262-055 051591. Rebuttal and supplemental information to rabbit teratology study noted above (-023 962354). Consists of protocol, dosing solution analyses results, ethoprop composition, and individual raw data photocopied from laboratory notebook; supplemental information upgrades study to complete and acceptable. (Martz, 6/17/87).

Summary: In study 962354, a slight but transitional weight loss was the only "effect" (observed at $\geq$ 0.5 mg/kg). A similar effect was not observed when the study was repeated (085901) at doses up to 2.5 mg/kg. In addition, a rangefinding study was performed and no effects were observed at $\leq$ 2.0 mg/kg (the next highest dose where effects were observed was 5.0 mg/kg). Therefore, CDFA considers the NOAEL to be > 2.5 mg/kg, and the NOEL = 2.5 mg/kg (M. Silva, 11/90).

GENE MUTATION

Microbial Systems

262-004 962370, "Mutagenicity Evaluation of MSTR-64-76 (Ethoprop Technical) Final Report," (Litton Bionetics, 10/4/76). Ethoprop (97.5%) tested at 0.001, 0.01, 0.1, 1.0, and 5.0 ul/plate +/- S9 on Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100. UNACCEPTABLE, single plates, no evidence of cytotoxicity, no increase in inversion rate. (Gee, 4/12/87).
EPA one-liner: No grade, negative effect.

262-055. Rebuttal response to above study (record #962370) by consultant toxicologists who agree with CDFA review and further state that "...we cannot defend the acceptance of this study;" no change in study status. (Martz, 6/30/87).

**262-058 058399, "Ames Salmonella/Microsome Plate Test (EPA/OECD)." (Pharmakon Research International, PH 301-RP-001-85, 8/9/85). Ethoprop, sp. gravity 1.094; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation at 0, 10, 33, 100, 333 or 1000 ug/plate, in triplicate, single trial; cytotoxicity test at 1666 and 5000 ug/plate showed inhibition of growth; report includes raw data for preparation of test solutions; no increase in reversion rate. ACCEPTABLE. (Gee, 5/5/88).

Mammalian Cells

**262-024 962367, "Murine Lymphoma; Mutagenesis Assay, Heterozygous at the Thymidine Kinase Locus for Determination of the Potential Mutagenicity of Ethoprop," (Mobil, NJ, 8/24/81). Ethoprop (technical) tested at 0.0316, 0.042, 0.056, 0.075, 0.100, 0.133, 0.180, and 0.237 ul/ml without S9, 0.0032, 0.0042, 0.0056, 0.0075, 0.0099, 0.0133, 0.0177, 0.0237, and 0.0316 ul/ml with S9 with mouse lymphoma (L5178Y) cells; No increase in mutation frequency reported. ACCEPTABLE. (Gee, 4/11/85).

**262-058 058401, "CHO/HGPRT - Mammalian Cell Forward Gene Mutation Assay." (Pharmakon Research International, PH 314-RP-001-85, 8/9/85). Ethoprop, lot 304295001 [see CDFA Record # 058399 for sp. gravity]; tested with CHO-K1-BH4 with and without rat liver

activation; concentrations without activation were 0, 50, 100, 150, 200, 250, 300, 350, 400 and 500 ug/ml, 5 hours, duplicate cultures; with activation at 0, 5, 10, 25, 50, 75, 100, 125 and 150 ug/ml, 5 hours; survival determined 19 hours after treatment, 7 days expression time for TG mutants; plated five 100 mm plates for mutation frequency per initial culture, 3 additional plates for cloning efficiency; cytotoxicity at 400 mg/ml and above; no evidence for increase in forward mutation frequency with treatment. ACCEPTABLE. (Gee, 5/5/88).

CHROMOSOME

262-024 962368, "Metaphase Analysis of Rat Bone Marrow Cells Treated In Vivo with Ethoprop," (Mobil, 8/27/81). Ethoprop (95.7%) tested at 2.0, 9.0 and 20.0 mg/Kg by oral gavage in Sprague-Dawley rats in bone marrow test; 6 males/group; UNACCEPTABLE, no females were used and no evidence of toxicity at the high dose which was the LD_{10}. Dosed for five days and sacrificed 6 hours after the last dose. Not upgraded by rebuttal in -055 noted below. No adverse effect indicated. (J.Gee, 4/12/85 and 7/1/87).

262-055. Rebuttal to bone marrow study noted above (#962368); no change in study status. (Gee, 7/1/87).

****262-024 962371**, "Activity of T1688 in the Dominant Lethal Assay in Rodents," (Microbiological Assoc., 9/17/81). Ethoprop (technical) was tested in the dominant lethal test at 2, 9, and 20 mg/Kg by oral gavage for 5 consecutive days with Sprague-Dawley rats; 10 males/group including a TEM positive control group; NOEL not established because an effect was seen at all doses with preimplantation losses (week 3) and death of implants (weeks 1-6), especially at 20 mg/kg. Males were mated 1:2 for 7 weekly intervals. Originally reviewed as unacceptable, but was upgraded by rebuttal response in -055 to ACCEPTABLE with **possible adverse effect**. (Gee, 4/12/85 and 7/1/87).

262-055. Rebuttal to dominant lethal study above (#962371); with the submission of characterization of the test material, CDFA # 51584 in 262- 055 and consideration of the rebuttal, the study is upgraded with a possible adverse effect. (Gee, 7/1/87).

262-076 065941. Exact duplicate of 962371.

**262-073 062429, "Dominant Lethal Study of Ethoprop Technical Administered Orally via Gavage to Cr1:COBS®CD®(SD)BR Male Rats," (ARGUS 218-004; Argus Research Laboratories, Inc., Horsham, PA; 07/28/87). Ethoprop, 95%, in 0.5% carboxymethyl cellulose, 5 ml/kg bw; 0, 1, 5, or 20 mg/kg by oral gavage for 5 days to 24 males/dose; each male mated to 2 females/week for 8 weeks; females sacrificed on day 14 of presumed gestation; adequate positive control; parental male NOEL = 5 mg/kg (3/25 died, organophosphate syndrome, and weight loss at 20 mg/kg); no dominant lethal effect observed; no adverse effect; study ACCEPTABLE. (Morris/Parker, 04/19/88).

262-073 062429. Also contains registrant's statements (dated 07/28/87) about CDFA's evaluation of study.

Comment: A possible dominant lethal effect was indicated in a first study(CDFA doc. # 262-024, rec. # 962371) but no adverse effect was demonstrated in a second study (CDFA doc. # 262-073, rec. # 062429). Registrant has submitted comments (CDFA doc. # 262-073, rec. # 062429, registrant's statements dated 07/28/87) on CDFA's findings of an adverse effect in the

first study. These statements contain neither additional data nor acceptable rationale for changing CDFA's finding of an adverse effect and no NOEL in the first study. Although interpretation of the two studies appears to conflict, an acceptable study or any sound piece of evidence that indicates a possible adverse effect cannot be ignored and therefore the study status of "possible adverse effect" stands. (Morris, 5/88).

****262-058 058403**, "In vitro Chromosome Aberrations Analysis in Chinese Hamster Ovary (CHO) Cells." (Pharmakon Research International, PH 320-RP-001-85, 10/26/85). Ethoprop, lot No. 304295001, sp. gravity = 1.094; tested with CHO cells without activation at 0, 50, 150 or 300 mg/ml, 5 hours followed by 14 - 18 hours incubation; with rat liver activation at 0, 10, 30 or 60 mg/ml in trial 1 and at 0, 50, 55, 60, 65 or 70 mg/ml in trial 2; positive for clastogenic effect at all concentrations in trial 2 with activation and at 60 mg/ml with activation in trial 1; **possible adverse effect**. ACCEPTABLE. (Gee, 5/6/88).

In the EPA 1988 reregistration standard, EPA requested an acceptable in vivo chromosome study to confirm these in vitro findings. (Gee, 3/22/89).

DNA DAMAGE

**262-024 962372, "Evaluation of Mobil #1238101 (Ethoprop Technical) in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay," (Litton Bionetics, 7/81, 2478-80). Ethoprop (95.7%) tested in UDS assay at 2.5, 5.0, 10.0, 25.0, 50.0, and 100 nl/ml on Fischer 344 rat cells; nuclear grain count determined for 50 cells/slide with 150 cells total; no mutagenic effects reported. ACCEPTABLE. (Gee, 4/12/85).

**262-058 058402, "Rat Hepatocyte Primary Culture/DNA Repair Test." (Pharmakon Research International, PH 311-RP-001-85, 8/9/85). Ethoprop, lot no. 304295001, sp. gravity = 1.094; tested with primary hepatocytes from a male Fisher 344 rat at 0, 0.33, 1.0, 3.3, 10, 33, 100, 333, 1000, 3333 and 10,000 ug/well with 2 ml medium, 18 - 20 hours exposure, grain counts by autoradiography; triplicate cultures, scored 50 cells per coverslip for a total of 150 cells; net nuclear counts; no evidence of increase in unscheduled DNA synthesis up to 100 ug/well - $\geq$ 333 ug/well was cytotoxic. ACCEPTABLE. (Gee, 5/6/88).

****262-058 058404**, "In vitro Sister Chromatid Exchange in Chinese Hamster Ovary (CHO) Cells." (Pharmakon Research International, PH 319-RP-001-85, 4/23/86) Ethoprop, lot 304295001; tested without activation at 0, 5, 50, 100, 200 and 350 ug/ml and with activation, trial 1, at 0, 5, 15, 30, 50, 55 and 60 ug/ml and at 0, 50, 60, 65, 70 and 75 ug/ml in trial 2, 5 hours treatment followed by 29 additional hours of incubation; percent of cells in first, second and third mitoses were scored; 50 metaphases per concentration (25 from each culture) were scored for sister chromatid exchanges; no increase in SCE's were noted without activation; statistically significant increases were found in both trials in the presence of rat liver activation; **possible adverse effect**. ACCEPTABLE. (Gee, 5/6/88).

NEUROTOXICITY

262-004 962351, "Neurotoxicity Test - Hens - Technical VC 9-104 - Final Report," (Hazleton, 6/15/67). Ethoprop (assumed purity of 100%) tested at 5.62 mg/kg (ten hens), with TOCP (ten hens) positive controls and four negative control hens; UNACCEPTABLE, no individual observations, no redosing at 21 days when no signs of delayed toxicity were seen. Acute toxicity

in that 4/10 died - inadequate number of hens. No adverse effect indicated. Atropine administered i.m. to hens in distress but these were not specifically identified. (Gee, 4/12/85).
EPA one-liner: Supplemental, negative effect.

262-060 051509, "Acute Delayed Neurotoxicity Study with Ethoprophos in the Domestic Hen," (Huntingdon Research Centre, 8/6/86). Technical ethoprop, 94.5%, to 63 hens by oral gavage in corn oil at 6.5 mg/kg (= LD_{--} determined by lab) with repeat at 5.3 mg/kg on day 21, with positive control = TOCP at 500 mg/kg to 10 hens, and negative control = vehicle to 10 hens; with ethoprop, 70% mortality by day 4 in spite of atropine and/or 2-PAM protection (reason for reduction of second dose); no clinical signs of delayed neurotoxicity (locomotor ataxia); no evidence of nerve damage in 16 survivors examined microscopically. Complete and ACCEPTABLE,** no adverse effect. (Martz, 6/25/87).

** 105 130418 "Acute Neurotoxicity Study with Ethoprop in Rats," (Weiler, M.S., Hazleton Wisconsin, Inc., Madison, WI; Laboratory Project ID: HWI 6224-200; 4/8/94). Ethoprop technical (96.2% pure) was administered by gavage in a single dose to Crl:CDBR VAF/plus rats (17/sex/dose) at 0 (corn oil) 5, 25 (females only), 50 and 75 (males only) mg/kg. Animals were observed and tested for 15 days post-dosing. NOEL = 50 mg/kg (males) and 25 mg/kg (females). Deaths occurred in both sexes at the high doses. Clinical signs were observed in males at $\geq$ 50 mg/kg and in females at $\geq$ 25 mg/kg during days 1-18 post-dosing. Male bodyweights were significantly decreased 8 days post-dosing. Both sexes showed effects from the FOB at $\geq$ 50 mg/kg in males and at $\geq$ 25 mg/kg at 2 hours post-dose. Motor activity was decreased in males at $\geq$ 50 mg/kg and in females at 50 mg/kg. There were no macro or microscopic lesions observed which would indicate neurotoxicity. ChE NOEL < 5 mg/kg in both sexes (plasma and RBC) day 2 post-dosing. These effects were reversed and there were no effects observed in brain ChE when animals were tested at 15 days post-dosing. Acceptable. M. Silva, 1/25/95.

107 134404 "Acute Oral Gavage Study with Ethoprop in Rats: Time-related Effects of Ethoprop on Brain, Plasma, and Red Blood Cell Cholinesterase Activities," (Weiler, M.S., Project #: HWI 6224-209; Hazleton WI, Inc., Madison, WI; 9/23/94). Ethoprop technical (95.7% pure) was administered by gavage (1 dose) to Crl:CD(SD)BR VAF/Plus rats (24/sex/dose) at 0, 30 or 60 mg/kg (males) and 20 or 40 mg/kg (females). Acute Systemic NOEL = 30 mg/kg - males; no NOEL - females (One male was sacrificed moribund. Both sexes had lower bodyweights at the high doses. Males at 60 mg/kg and females at $\geq$ 20 mg/kg showed treatment-related clinical signs.) **Possible adverse effect:** A ChE NOEL was not achieved in either sex (Plasma, RBC and brain ChE were significantly decreased at all treatment levels by day 1. These effects showed signs of reversal at day 15 but were not completely reversed in RBC and brain.) These data are supplemental. M. Silva, 3/7/95.

** 106 134403 "13-Week Dietary Neurotoxicity Study with Ethoprop in Rats," (Weiler, M.S., Project ID: HWI 6224-199; Hazleton Wisconsin, Inc., Madison, WI; 9/21/1994). Ethoprop technical (95.7% pure) was fed in the diet to Crl:CD BR VAF/Plus rats (27/sex/dose) at 0 (diet only), 4, 40 and 400 ppm for 13 weeks. Of the 27/sex/dose, 12/sex/dose were used for the FOB and 15/sex/dose were used for a ChE assay. Systemic NOEL = 40 ppm (At 400 ppm, both sexes showed decreased body weights. Food consumption was transitionally decreased in both sexes. Males at 400 ppm showed perianal brown haircoat that was test material related.) Neurotoxicity NOEL = 40 ppm (At 400 ppm, decreased capacity in the FOB (decreased mean analgesic reflex times, hindlimb grip strength in males) and motor activity tests were observed.) ChE NOEL < 4 ppm (ChE levels were decreased in RBC and Brain at $\geq$ 40 ppm throughout the study and in plasma at $\geq$ 4 ppm.) No adverse effects. Acceptable. M. Silva, 3/3/95.

108 134406 This volume is an exact copy of 105 130418, reviewed above.

262-136; 159626; “Acute Oral Toxicity Study with Ethoprop and Three Ethoprop Metabolites (O-ethyl-S-methyl-S-propylphosphorodithioate, O-ethyl-O-methyl-S-propylphosphorothioate, and O-ethyl-S-propylphosphorothioate) in Rats with Determination of Effects on Cholinesterase Activity”; (M.S. Weiler; Covance Laboratories Inc., Madison, WI; Project No. 6224-246; 1/20/98); Study was performed in two phases. In Phase 1, 10 female rats/group were orally gavaged with 4 doses of ethoprop, ranging from 20 to 75 mg/kg, with 6 doses of O-ethyl-S-methyl-S-propylphosphorodithioate (SME), ranging from 20 to 200 mg/kg, with 6 doses of O-ethyl-O-methyl-S-propylphosphorothioate (OME), ranging from 5 to 200 mg/kg, and 5 doses of O-ethyl-S-propylphosphorothioate (M1) ranging from 250 to 2000 mg/kg. Clinical signs included thin appearance, staggered gait, hypoactivity, red-stained face, excessive salivation, dyspnea, lacrimation, miosis, soft stool, tremors and absence of pain reflex. LD50 (95% confidence limits): Ethoprop (F) 55.8 (48.9 to 63.6) mg/kg, SME (F) 50.0 (41.0 to 61.0) mg/kg, OME (F) 22.4 (19.2 to 26.1) mg/kg, M1 (F) 1608 (1253 to 2064) mg/kg. In Phase 2, 10 females/group were dosed orally with 0 (corn oil), 19 mg/kg (ethoprop), 17 mg/kg (SME) or 8 mg/kg (OME) (based upon 1/3 of LD50 dose level) and the plasma, rbc and brain cholinesterase (ChE) activities measured 24 hours after dosing. For ethoprop, mean plasma, rbc and brain ChE activities were 26.5, 63.0 and 67.7% of control values. For SME, mean plasma, rbc and brain ChE activities were 22.0, 70.3 and 29.0% of control values. For OME, the respective activities were 59.7, 52.8 and 51.6% of control values. **Study supplemental.** (Moore, 3/26/98)